

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Petkovich *et al.*
Serial No.: 09/668,482
Filing Date: September 25, 2000
Title: Retinoid Metabolizing Protein
Art Unit: 1652
Examiner: Elizabeth Slobodyansky, Ph.D.
Atty's Docket No.: 32391-2005

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OCT 15 2003

The Commissioner of Patents and Trademarks
Washington, D.C. 20331
U.S.A.

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this correspondence, totaling 70 pages, is being facsimile transmitted at 703.872.9306 to the USPTO on the date set forth below:


John C. Hunt, Registration No. 36,424

October 15, 2003

Date

CONFIDENTIALITY NOTE:

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John Hunt
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Thank you

PETITION UNDER 37 CFR §§ 1.181 & 1.182

Dear Sir:

This is a petition made in a situation not specifically provided for in the regulations. The undersigned submitted a response to an action on August 11, 2003, and the PTO failed to deduct required fees from Applicant's Attorney's Deposit account, as authorized in the response. In view of the detail d

statement of facts set out below, the undersigned hereby requests the PTO to deduct the required fees from the Deposit account and to accept the response as timely received.

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Statement of Facts

OCT 15 2003

Timeline of events:

1. A non-final action was issued by the PTO on February 13, 2003, copy included as Exhibit A.
2. The undersigned submitted a response to the action to the PTO by facsimile on August 11, 2003. A copy of the response, which included a petition for extension of time, is included as Exhibit B.
3. On August 19, 2003, the PTO mailed a notification of "Informality re payment of fee" to the undersigned at the address of his former firm, Blake, Cassels & Graydon LLP. A copy is included as Exhibit C.
4. On September 3, 2003, the undersigned submitted a Power of Attorney in his favor. Included as Exhibit D is the complete submission with a copy of the receipt card date stamped by the PTO.
5. On October 14, 2003 the undersigned's former firm faxed a copy of the PTO notification of August 19, 2003 to the undersigned at his current address. A copy of the fax is included as Exhibit E.

Points to be reviewed and action requested:

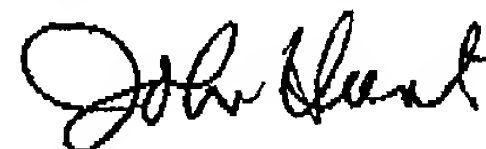
6. The PTO notification of August 19, 2003 indicates that "the amendment is considered incomplete in that the funds in Deposit Account No. are insufficient to cover the entire fee due. A period of one month was granted for responding to the notification, which period ended on September 19, 2003.
7. Included as Appendix F is a copy of the Deposit Account Statement for Deposit Account No. 502,651, as obtained from the PTO Web site on October 14, 2003. The Statement indicates that for the entire month of

- August, the balance in the account did not go below \$1,655.00.
8. As indicated in Applicant's Petition for extension of time, included as part of Exhibit B, the box which states "the Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 502651" is checked.
 9. Applicant thus submits that the PTO was properly authorized to charge all required fees to Deposit Account Number 502651 and that the account included sufficient fees.
 10. Applicant hereby requests that: the extension fee of \$930.00 be deducted from Deposit Account Number 502651; the IDS fee of \$180.00 be deducted from Deposit Account Number 502651; that the PTO notification be withdrawn as though it had never been issued; and Applicant's response of August 11, 2003 be entered and returned to the Examiner for further prosecution. Applicant further requests that, if a notice of abandonment has been issued by the PTO, that such notice also be withdrawn.
 11. The Director is hereby authorized to charge any other fee which may be required for this submission, including any petition fee, or credit any overpayment, to Deposit Account Number 502651.

Should any Patent Office Official want to telephone, the call should be made to John C. Hunt (Registration No. 36,424) at (416) 865-8281.

October 15, 2003
Date

Yours very truly,



John C. Hunt
Registration No. 36,424

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OCT-15-2003 11:21

TORYS LLP TORONTO

416 865 7380

P.04

Exhibit A

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TORYS LLP TORONTO

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UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/668,482	09/25/2000	P. Martin Petkovich	57600/00035	3039

7590 02/13/2003

John C Hunt Blake Cassels & Graydon
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P O Box 25
Toronto, ON M5L 1A9
CANADA

EXAMINER

SLOBODYANSKY, ELIZABETH

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 02/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary

Applicati n N .

09/668,482

Applicant(s)

PETKOVICH ET AL.

Examiner

Elizabeth Slobodyansky

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 83-95,97-102 and 104-112 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 83-95,97-102, 104-112 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.65(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 13.
- 4) ☐ Interview Summary (PTO-419) Paper No(s) ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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DETAILED ACTION

The finality of the Office action mailed August 13, 2002 is hereby withdrawn in view of the new ground(s) of rejection.

Claims 83-95, 97-102 and 104-112 are pending.

During a telephone conversation conducted on February 12, 2003, Dr. John Hunt requested an extension of time for three MONTH(\$) and authorized the Commissioner to charge Deposit Account No. 02-2553 the required fee of \$ 920.00 for this extension.

Specification

The disclosure is objected to because of the paper and computer readable forms of the Sequence Listing are not identical. The paper copy contains 35 sequences while the computer readable form has 43 sequences.

A substitute paper copy of the Sequence Listing identical to the computer readable form in the file is required. It should be accompanied by the statement the two forms are identical and by the amendment directing the entry of a substitute Sequence Listing.

Claim Objections

Claims 83, 89 and 90 are objected because of the following.

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In claims 83 and 90, the proper recitation of the Markush group requires "or" before the last member of the group (line 8).

Claim 89 is objected because of the following. The Markush group requires "or" before "SEQ ID NO:32" at two occurrences.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 97-102 and 104-112 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims encompass all polypeptides of any function or that oxidize/hydroxylate retinoid and that bind to any antibody specific for SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:32. The Examiner is unable to locate adequate support in the specification for such polypeptides. Thus there is no indication that polypeptides encompassed by claims 97-102 and 104-112 were within the scope of the invention as conceived by Applicants at the time the application was filed.

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Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

Claims 83, 85-90, 92-95, 97-102 and 104-112 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite "a conservatively substituted amino acid variant" of the amino acid sequences encoded by SEQ ID NOs: 3, 5 or 31 or encoded by a DNA that hybridizes thereto or to a degenerate variant thereof under specific conditions. This amounts to any structure having the same function as a protein encoded by SEQ ID NOs: 3, 5 or 31. The structural limitations are insufficient because while a substitution is required to be conservative any amino acid residue in the sequence and any number thereof can be substituted resulting in a completely novel structure that is not described. This is equivalent to a claim with no structural limitations wherein an enzyme is defined by the function only. Furthermore, the function described only as "oxidizes/hydroxylates a retinoid" encompasses many different activities and substrate specificities. In addition, a genus of degenerate variants of SEQ ID NOs: 3, 5 or 31 is enormous.

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Claims 83, 85-90, 92-95 and 107-112 are directed to polypeptides that oxidize or hydroxylate a retinoid or retinol or retinoic acid or *all-trans* retinoic acid at any position. Therefore, they encompass a genus of polypeptides described by broad function. The specification teaches only one species of the claimed genus, an *all-trans* retinoic acid hydroxylase that specifically hydroxylates *all-trans* retinoic acid at the C4-and the C18-position of the β -ionone ring and oxidizes *all-trans* retinoic acid at the C4-position of the β -ionone ring. The specification does not teach polypeptide species with any other retinoid oxidizing/hydroxylating activity, i.e, said activity with substrate specificity as broad as any retinoid, i.e., retinoic acid (RA), retinal, retinol in every stereo configuration as well as undescribed natural and artificial variants thereof (see the specification, paragraph bridging pages 5 and 6).

Furthermore, according to the definition of "retinoid", the genus of retinoids encompasses "a group of compounds which includes retinoic acid, vitamin A (retinol) and a series of natural and synthetic derivatives that an exert profound effects on development and differentiation in a wide variety of systems" (specification, paragraph bridging pages 4 and 5). The specification does not discloses any species within the genus of retinoids other than naturally occurring retinoic acid and derivatives thereof. There is no description of any synthetic derivative thereof or any natural or synthetic compound that can be construed as exerting profound effects on development and differentiation in a wide variety of systems. Therefore, the genus of retinoids

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encompasses compounds of different structures and functions and the specification fails to disclose the correlation between structure and function common to all members of the genus.

In addition, claims 97-102 and 104-106 are drawn to a polypeptide that binds to an antibody specific for SEQ ID NOs: 2, 4 or 32 or is encoded by a DNA that hybridizes to the DNA encoding thereof and has no known function.

Therefore, the claims are drawn to a genus of polypeptides of undefined structures having any function.

The genus of polypeptides that comprises these above polypeptide molecules is a large variable genus encompassing many different proteins and fragments thereof. Many structurally and functionally unrelated polypeptides are encompassed within the scope of these claims, including partial sequences. Said genus encompasses both polypeptides having an enzymatic activity and inactive variants thereof as well polypeptides with undisclosed function. The specification fails to provide identifying characteristics and/or correlation between structure and function common to all members of the genus.

Furthermore, claims 85 and 92 are drawn to polypeptides encoded by nucleotide sequences that are part of fish genome. This part of rejection comprises polypeptides with a narrow function such as a retinoic acid inducible polypeptides having all-*trans*

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retinoic acid 4-hydroxylase. The specification teaches only a single species of the claimed diverse genus, an all-*trans* retinoic acid 4-hydroxylase from zebrafish. The recitation of "fish genome" fails to provide a sufficient description of the claimed genus of proteins as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. The CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "In claims to genetic material, however a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus". Similarly with the claimed genus of proteins the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the protein species within the genus from other proteins such that one can visualize or recognize the identity of the members of the genus.

Thus, a polypeptide other than a polypeptide having 1) all-*trans* retinoic acid 4-hydroxylase activity and 2) an amino acid sequence of SEQ ID NO: 2, 4 or 32 or that is encoded by a DNA that hybridizes under highly stringent conditions to SEQ ID NO:3, 5

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or 31 lacks sufficient written description needed to practice the invention of claims 83-95, 97-102 and 104-112.

Claims 83, 85-90, 92-95, 97-102 and 104-112 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a all-trans retinoic acid 4-hydroxylase encoded by SEQ ID NOs: 3, 5 or 31 or encoded by a sequence that hybridizes thereto under highly stringent conditions, does not reasonably provide enablement for a conservatively substituted amino acid variant thereof, a retinoid oxidase of any substrate specificity that is encoded by a sequence that hybridizes to SEQ ID NOs: 3, 5 or 31 or a degenerate variant thereof and a conservatively substituted amino acid variant thereof as well as a polypeptide that oxidizes/hydroxylates retinoid or having unknown function that binds to an antibody specific for SEQ ID NOs: 3, 5 or 31. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broader than the enablement provided by the disclosure with regard to the huge number of all possible derivatives having the desired enzymatic activities.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.

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1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Factors pertinent to this discussion include predictability of the art, guidance in the specification, breadth of claims, and the amount of experimentation that would be necessary to use the invention.

Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claim, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is

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unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any sequence that is claimed in claims 83, 85-90, 92-95, 97-102 and 104-112 because the specification does not establish: (A) regions of the protein structure which may be modified without effecting the requisite activity. The specification does not teach the structure that is responsible for a specific all-trans retinoic acid 4-hydroxylase activity as compared to any other retinoid oxidizing activity; (B) the general tolerance of a protein to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. This reasoning is also applicable to cytochrome P450 structures comprising the heme binding region because there is no guidance provided as to what are residues that are responsible for the substrate specificity of the enzymes of the instant invention.

Furthermore, degenerate variants of SEQ ID NOs: 3, 5 or 31 encompass an enormous number of molecules. The specification does not provide any guidance as to

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which of these degenerate variants can be used, so that a DNA that hybridizes thereto would encode a protein with the requisite properties.

With regard to claims 85 and 92, the rejection applies because the specification enables only for polypeptides that are encoded by DNAs that hybridize to SEQ ID NO: 3, 5 or 31 under highly stringent conditions, it does teach how to obtain variant polypeptides of unknown homology to SEQ ID NO:2, 4 or 32.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a number of amino acid modifications of SEQ ID NOs: 2, 4 or 32. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of a protein having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Claims 97-102 and 104-106 are drawn to proteins with no function. Applicants have not provided sufficient guidance as to what is the function of proteins encompassed by the claims.

The state of the art does not allow the predictability of the properties based on the structure. Therefore, one skilled in the art would require guidance as to how to use a polypeptide of unknown function that binds to an antibody specific for SEQ ID NOs: 2,

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4 or 32 or is encoded by a DNA that hybridizes to a DNA encoding thereof in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 83-95, 97-102 and 104-112 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 83-90, 92-95 recite "conservatively substituted amino acid variant thereof". There are no clear assigned definitions of the term "conservatively substituted amino acid variant" in the art.

Claims 97-102 and 104-112 are confusing because they recite an antibody that is elicited by SEQ ID NO:2, 4 or 32 and by an epitope of unknown structure.

Claims 83-86, 89-92, 95 and 107-112 recite "retinoid". This term is defined as comprising "a series of natural and synthetic derivatives" (emphasis added). The metes and bonds of "derivative" are neither disclosed in the specification nor clearly known in the art.

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Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 83-95, 97-102 and 104-112 are rejected under 35 U.S.C. 102(b) as being anticipated by Duell et al. (1992).

Duell et al. (form PTO-1449 filed February 6, 2003, reference 6, J. Clin. Investigation (1992), 90,1269-1274) teach a retinoic acid induced all-*trans* retinoic acid 4-hydroxylase activity in human skin microsomes. They teach that said activity catalyzes conversion of RA to 4-OH RA and 4-oxo RA (abstract, page 1271).

The microsomal fraction having the requisite activity contains a polypeptide with said activity. Said peptide is "isolated" from its natural environment. Therefore, the Duell et al. reference anticipates claims 83-95, 97-102 and 104-112.

Claims 83-95, 97-102 and 104-112 are rejected under 35 U.S.C. 102(b) as being anticipated by Duell et al. (1994).

Duell et al. (form PTO-1449 filed February 6, 2003, reference 6, J. Investigative Dermatology (1994), Vol. 102, page 641, SID abstracts, abstract 704) teach a unique

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cytochrome P450 that has retinoic acid induced all-trans retinoic acid 4-hydroxylase activity but does not metabolize 9-cis or 13-cis retinoic acid. They demonstrated said activity in human skin microsomes.

The microsomal fraction having the requisite activity contains a polypeptide with said activity. Said peptide is "isolated" from its natural environment. Therefore, the Duell et al. reference anticipates claims 83-95, 97-102 and 104-112.

Claims 97, 99, 101 and 104-112 are rejected under 35 U.S.C. 102(b) as being anticipated by Vetter et al.

Vetter et al. teach the amino acid sequence of an inducible cytochrome P-450 protein from Periwinkle (*Catharanthus roseus* L.) (page 1002, Figure 3.). Since an epitope is not limited to a specific fragment, this polypeptide will bind to an antibody elicited by an epitope of some five, for example, amino acids within the conserved region of SEQ ID NOs: 2, 4 or 32 and, therefore anticipates claims 97, 99, 101 and 104-112.

Claims 97, 99, 101 and 104-112 are rejected under 35 U.S.C. 102(b) as being anticipated by Shen et al.

Shen et al. teach the amino acid sequence of a mouse cytochrome P-450 protein (page 11485, Figure 3.). Since an epitope is not limited to a specific fragment,

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this polypeptide will bind to an antibody elicited by an epitope of some five, for example, amino acids within the conserved region of SEQ ID NOs: 2, 4 or 32 and, therefore anticipates claims 97, 99, 101 and 104-112.

Response to Arguments

Applicant's arguments filed May 31, 2002 have been fully considered but they are not persuasive.

Applicants argue that claims 97-102 and 104-112 do not introduce the new matter because the specification on page 36 teaches that "antibodies can be used to detect the proteins of the invention, portions thereof or closely related isoforms in various biological materials" (page 10). This is not persuasive because there is support for an antibody and a method of use thereof but not for proteins that can be detected using said antibodies.

With regard to conservative variants, applicants disagree that they amount to any protein having the desired function (pages 11-12). Applicants assert that "it is only conservatively substituted variants of these proteins that are claimed. The claim includes only those variant proteins in which an individual amino acid is substituted for another amino acid of protein to have function. ... while it is admitted there is no limitation on the number of such substitutions that might be made, any such substitution is clearly based on one of basic claimed structures(a protein encoded by the sequence

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that hybridizes to SEQ ID NO:3, 5, etc.) and would be known to the skilled person" (page 12, 2nd paragraph). This is not persuasive because claims are not drawn to proteins having substitutions from other proteins. Ad in any event, there is no limitation on the number and location of residues to be substituted.

Applicants further argue with regard to the function that "applicants reasonable expect that P450RAI oxidizes the 18 position of the β -ionone ring as well as the 4 position, and that P450RAI oxidizes retinol as well as RA (see page 3, lines 23-26)" (page 13, 2nd paragraph). The specification on page 3, lines 23-26 reads differently. However, on page 3, lines 27-30, it provides support for the 4 position of β -ionone ring of RA. However, the claims recite much broader specificity expanding the scope of the claims to encompass retinoid oxidizing enzymes of different function and properties. With regard to the 102 rejection, applicants argue that "the antibody is elicited by an epitope located within a specified unconserved region of the protein" (page 17). This is not persuasive because within this region the proteins of the instant invention share a few identical or conservatively substituted amino acids with the proteins of the references. An antibody elicited by such fragment would cross react with many proteins including the proteins of the instant invention and the references.

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Conclusion

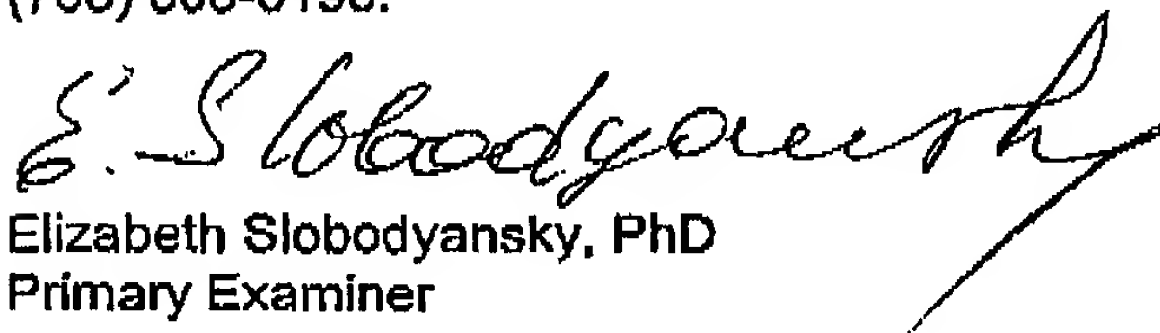
The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Frolik et al. (1979, form PTO-1449 filed February 6, 2003, reference 8) teach *all-trans* retinoic acid 4-hydroxylase activity in hamster trachea and liver.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.


Elizabeth Slobodyansky, PhD
Primary Examiner

February 12, 2003

Substitute for form 1449A/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)		Complete if Known	
		Application Number	09/668,482
		Filing Date	September 25, 2000
		First named Inventor	PETKOVICH
		Group Art Unit	1652
		Examiner Name	SLOBODYANSKY, E.
Sheet	1	of	5
		Atty Docket Number	57600/00035

OTHER DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, page(s), volume-issue number(s), publisher, city and/or country where published	T ²
ES	1	ADAMSON P.C. et al., "Time Course of Induction of Metabolism..." Cancer Research, 53: 472-476 (1993).	
	2	BOYLAN J.F. et al., "Targeted Disruption of Retinoic Acid Receptor..." Molecular and Cellular Biology, 15: 2, 843-851 (Feb. 1995).	
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	6	DUELL, E.A. et al., "Human skin levels of retinoic acid and cytochrome P-450-derived 4-hydroxyretinoic acid after topical application of retinoic acid in vivo compared to concentrations required to stimulate retinoic acid receptor-mediated transcription in vitro", J. Clin. Invest., 90: 1269-1274 (1992).	
ES	7	DUELL, E.A. et al., "All-trans, 9-cis and 13-cis retinoic acid each induce a cytochrome P450 4-retinoic acid hydroxylase which causes all-trans but not 9-cis or 13-cis retinoic acid to self-metabolize", SID Abstracts, 102: 641 (1994). <i>Investigative Dermatology</i>	
	8	FROLIK, C.A., et al., "Isolation and identification of 4-hydroxy- and 4-oxoretinoic acid. In vitro metabolites of all-trans-retinoic acid in hamster trachea and liver", Biochemistry, 18: 2092-2097 (1979).	
	9	MUINDI, J.R.F. et al., "Clinical pharmacology of all-trans retinoic acid", Leukemia, 8: S16-S21 (1994).	
	10	ROBERTS, A.B. et al., "In vitro metabolism of retinoic acid in hamster intestine and liver", J. Biol. Chem., 254: 6296-6302 (1979).	
	11	ROBERTS, A.B. et al., "Retinoid-dependent induction of the in vivo and in vitro metabolism of retinoic acid in tissues of the vitamin A-deficient hamster", J. Biol. Chem., 254: 6303-6309 (1979).	
	12	TAKATSUKA, J. et al., "Retinoic acid metabolism and inhibition of cell proliferation: an unexpected liaison", Cancer Res., 56: 675-678 (1996).	
	13	VAN WAUWE, J.P., et al., "Ketoconazole inhibits the in vitro and in vivo metabolism of all-trans-retinoic acid", J. Pharm. Exp. Ther. 245: 718-722 (1988).	
	14	VAN WAUWE, J.P. et al., "Effects of cytochrome P-450 inhibitors on the in vivo metabolism of all-trans-retinoic acid in rats", J. Pharm. Exp. Ther. 252: 365-369 (1990).	
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Examiner Signature	E. Slobodyansky	Date Considered	2/10/03
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute for form 1449A/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)		Complete if Known			
		Application Number	09/668,482		
		Filing Date	September 25, 2000		
		First named Inventor	PETKOVICH		
		Group Art Unit	1652		
		Examiner Name	SLOBODYANSKY, E.		
Sh et	2	of	5	Atty Docket Number	57600/00035

OTHER DOCUMENTS			
Examiner Initials	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, page(s), volume-issue number(s), publisher, city and/or country where published	T ²
<i>ES</i>	16	WILLIAMS, J.B., et al., "Inhibition of retinoic acid metabolism by imidazole antimycotics in F9 embryonal carcinoma cells", Biochem. Pharm. 36: 1386-1388 (1987).	
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	20	AKIMENKO, M.-A. et al., "Differential induction of four msx homeobox genes during fin development and regeneration in zebrafish", Development, 121: 347-357 (1995).	
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	22	BLUMBERG, B. et al., "Novel retinoic acid receptor ligands in Xenopus embryos", Proc. Natl. Acad. Sci. USA, 93: 4873-4878 (1996).	
	23	BOYLE, A.L. et al., "Rapid physical mapping of cloned DNA on banded mouse chromosomes by fluorescence in situ hybridization", Genomics 12: 106-115 (1992).	
	24	CASTONGUAY, A. et al., "Expression of xenobiotic-metabolizing enzymes in cultured rat tracheal epithelial cells", Environ. Health Perspect. 103: 254-258 (1995).	
	25	CHAMBON, P., "The molecular and genetic dissection of the retinoid signaling pathway", Recent Progress in Hormone Research, 50: 317-332 (1995).	
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	28	CREECH KRAFT, J. et al., "Temporal distribution, localization and metabolism of all-trans-retinol, dihydroretinol and all-trans-retinal during Xenopus development", Biochem J., 301: 111-119 (1994).	
<i>ES</i>	29	FIGIELLA, P.D. et al., "Expression of cellular retinoic acid-binding protein (Type II) in Escherichia coli", J. Biol. Chem., 268: 21545-21552 (1993).	

Examiner Signature	<i>E. Slobodyansky</i>	Date Considered	<i>2/10/03</i>
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Substitute for form 1448A/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)			Complete if Known	
			Application Number	09/668,482
Sheet 3 of 5			Filing Date	September 25, 2000
			First named Inventor	PETKOVICH
			Group Art Unit	1652
			Examiner Name	SLOBODYANSKY, E.
			Atty Docket Number	57600/00035

OTHER DOCUMENTS				
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, page(s), volume-issue number(s) publisher, city and/or country where published		T ²
ES	30	GREEN, S., et al., "A versatile in vivo and in vitro eukaryotic expression sector for protein engineering", Nucl. Acids Res., 16: 369 (1988).		
	31	GUBLER, M.L. et al., "Metabolism of Retinoic Acid and Retinol..." Methods in Enzymology, 189, 525-530 (1990).		
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ES	45	MARTINI, R. et al., "Participation of P450 3A enzymes in rat hepatic microsomal retinoic acid 4-hydroxylation", Arch. Biochem. Biophys. 303: 57-66 (1993).		

Examiner Signature	<i>E. Slobodyansky</i>	Date Considered	2/10/03
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

¹Unique citation designation number. ²Applicant is to place a check mark here if English language Translation is attached.

Substitute for form 1449A/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)		Complete If Known			
		Application Number	09/688,482		
		Filing Date	September 25, 2000		
		First named Inventor	PETKOVICH		
		Group Art Unit	1652		
		Examiner Name	SLOBODYANSKY, E.		
Sh et	4	of	5	Atty Docket Number	57600/00035

OTHER DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, page(s), volume-issue number(s), publisher, city and/or country where published	T ²
ES	46	MARTINI, R. et al., "Retinal dehydrogenation and retinoic..." Biochemical Pharmacology, 47, No. 5, 905-909, 1994.	
	47	MARIKAR, Y. et al., "Regulation, properties, and solubilization of a unique cytochrome P-450 that specifically metabolizes all-trans retinoic acid to less active 4-hydroxy retinoic acid in human keratinocyte HACAT cells", Abstract, J. Invest. Dermatol. 106(4): 807 (1996).	
	48	MONIA, B.P. et al., "Antitumor activity of a phosphorothioate antisense oligodeoxynucleotide targeted against C-raf kinase", Nature Med., 2: 668-675 (1996).	
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	56	OGURA, T. et al., "A retinoic acid-triggered cascade of HOXB1 gene activation", Proc. Natl. Acad. Sci. USA 92: 387-391(1995).	
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ES	59	RANER, G.M. et al., "Metabolism of all-trans, 9-cis, and 13-cis isomers of retinal by purified isozymes of microsomal cytochrome P450 and mechanism-based inhibition of retinoid oxidation by citral", Mol. Pharmacol. 49: 515-522 (1996).	

Examiner Signature	E. Slobodyansky	Date Considered	2/10/03
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¹Unique citation designation number. ²Applicant is to place a check mark here if English language Translation is attached.

Exhibit B

Page 1 of 29 pages

PTO/SB/21 (01-03)
Approved for use through 04/30/2003, OMB 0581-0031
U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

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TRANSMITTAL FORM (to be used for all correspondence after initial filing)	Application Number	09/668,482
	Filing Date	09/25/2000
	First Named Inventor	PETKOVICH, Martin P.
	Art Unit	1652
	Examiner Name	SLOBODYANSKY, Elizabeth
	Attorney Docket Number	32391-2005
Total Number of Pages in TTS Submission		279/26

ENCLOSURES (check all that apply)		
<input checked="" type="checkbox"/> Fee Transmittal Form	<input type="checkbox"/> Drawing(s)	<input type="checkbox"/> After Allowance Communication to Group
<input checked="" type="checkbox"/> Fee Attached	<input type="checkbox"/> Licensing-related Papers	<input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences
<input checked="" type="checkbox"/> Amendment/Reply	<input type="checkbox"/> Petition	<input type="checkbox"/> Appeal Communication to Group (Appeal Notice, Brief, Reply Brief)
<input type="checkbox"/> After Final	<input type="checkbox"/> Petition to Convert to a Provisional Application	<input type="checkbox"/> Proprietary Information
<input type="checkbox"/> Affidavit/Declaration(s)	<input type="checkbox"/> Power of Attorney, Revocation	<input type="checkbox"/> Status Letter
<input checked="" type="checkbox"/> Extension of Time Request	<input type="checkbox"/> Change of Correspondence Address	<input checked="" type="checkbox"/> Other Enclosure(s) (please identify below): Letter under 37 CFR 1.56
<input type="checkbox"/> Express Abandonment Request	<input type="checkbox"/> Terminal Disclaimer	
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<input type="checkbox"/> Response to Missing Parts under 37 CFR 1.52 or 1.53		

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT	
Firm or Individual	John Hunt, Registration No. 36,424
Signature	<i>John Hunt</i>
Date	08/11/2003

CERTIFICATE OF TRANSMISSION/MAILING - To 703.308.4242	
I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231 on this date: 08/11/2003	
Typed or printed	John Hunt
Signature	<i>John Hunt</i>
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This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to be (and by the USPTO is provided) an application. Confidentiality is guaranteed by 35 U.S.C. 122 and 37 CFR 1.54. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Washington, DC 20231.

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TRANSMITTAL FORM (to be used for all correspondence after initial filing)	Application Number	09/668,482
	Filing Date	09/25/2000
	First Named Inventor	PETKOVICH, Martin P.
	Art Unit	1652
	Examiner Name	SLOBODYANSKY, Elizabeth
	Attorney Docket Number	32391-2005
Total Number of Pages in This Submission		26

ENCLOSURES (Check all that apply)		
<input checked="" type="checkbox"/> Fee Transmittal Form <input checked="" type="checkbox"/> Fee Attached <input checked="" type="checkbox"/> Amendment/Reply <input type="checkbox"/> After Final <input type="checkbox"/> Affidavits/declaration(s) <input checked="" type="checkbox"/> Extension of Time Request <input type="checkbox"/> Express Abandonment Request <input checked="" type="checkbox"/> Information Disclosure Statement <input type="checkbox"/> Certified Copy of Priority Document(s) <input type="checkbox"/> Response to Missing Parts/Incomplete Application <input type="checkbox"/> Response to Missing Parts under 37 CFR 1.52 or 1.53	<input type="checkbox"/> Drawing(s) <input type="checkbox"/> Licensing-related Papers <input type="checkbox"/> Petition <input type="checkbox"/> Petition to Convert to a Provisional Application <input type="checkbox"/> Power of Attorney, Revocation <input type="checkbox"/> Change of Correspondence Address <input type="checkbox"/> Terminal Disclaimer <input type="checkbox"/> Request for Refund <input type="checkbox"/> CD, Number of CD(s) _____	<input type="checkbox"/> After Allowance Communication to Group <input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences <input type="checkbox"/> Appeal Communication to Group (Appeal Notice, Brief, Reply Brief) <input type="checkbox"/> Proprietary Information <input type="checkbox"/> Status Letter <input checked="" type="checkbox"/> Other Enclosure(s) (please identify below): Letter under 37 CFR 1.56
Remarks		
SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT		
Firm or Individual	John Hunt, Registration No. 36,424	
Signature	<i>John Hunt</i>	
Date	08/11/2003	

CERTIFICATE OF TRANSMISSION/MAILING TO 703.308.4242		
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Signature	<i>John Hunt</i>	Date 08/11/2003

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Washington, DC 20231.

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FEE TRANSMITTAL for FY 2003

Effective 01/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT (\$1,110.00)

Complete if Known

Application Number 09/668,482
 Filing Date 09/25/2000
 First Named Inventor PETKOVICH, Martin P.
 Examiner Name SLOBODYANSKY, Elizabeth
 Art Unit 1652
 Attorney Docket No. 32391-2005

METHOD OF PAYMENT (check all that apply)

☐ Check ☒ Credit card ☐ Money Order ☐ Other ☐ None
☐ Deposit Account:
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The Commissioner is authorized to: (check all that apply)

☐ Charge fee(s) indicated below ☒ Credit any overpayments
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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description	Fee Paid
1001 750	2001 375	Utility filing fee	
1002 330	2002 165	Design filing fee	
1003 520	2003 260	Plant filing fee	
1004 750	2004 375	Reissue filing fee	
1005 160	2005 80	Provisional filing fee	
SUBTOTAL (1)			(\$0.00)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

Total Claims -20** = X = \$0
 Independent Claims -3** = X = \$0
 Multiple Dependent = \$0

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description
1202 18	2202 9	Claims in excess of 20
1201 84	2201 42	Independent claims in excess of 3
1203 280	2203 140	Multiple dependent claim, if not paid
1204 84	2204 42	** Reissue independent claims over original patent
1205 18	2205 9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) (\$0.00)

**or number previously paid, if greater. For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description	Fee Paid
1051 130	2051 65	Surcharge - late filing fee or oath	
1052 50	2052 25	Surcharge - late provisional filing fee or cover sheet	
1053 130	1053 130	Non-English specification	
1812 2,520	1812 2,520	For filing a request for ex parte reexamination	
1804 920*	1804 920*	Requesting publication of SIR prior to Examiner action	
1805 1,840*	1805 1,840*	Requesting publication of SIR after Examiner action	
1251 110	2251 55	Extension for reply within first month	
1252 410	2252 205	Extension for reply within second month	\$930.00
1253 930	2253 465	Extension for reply within third month	
1254 1,450	2254 725	Extension for reply within fourth month	
1255 1,970	2255 985	Extension for reply within fifth month	
1401 320	2401 160	Notice of Appeal	
1402 320	2402 160	Filing a brief in support of an appeal	
1403 280	2403 140	Request for oral hearing	
1451 1,510	1451 1,510	Petition to institute a public use proceeding	
1452 110	2452 55	Petition to revive - unavoidable	
1453 1,300	2453 650	Petition to revive - unintentional	
1501 1,300	2501 650	Utility issue fee (or reissue)	
1502 470	2502 235	Design issue fee	
1503 630	2503 315	Plant issue fee	
1480 130	1480 130	Petitions to the Commissioner	
1807 50	1807 50	Processing fee under 37 CFR 1.17(a)	\$180.00
1806 180	1806 180	Submission of Information Disclosure Stmt	
8021 40	8021 40	Recording each patent assignment per property (times number of properties)	
1809 750	2809 375	Filing a submission after final rejection (37 CFR 1.129(a))	
1810 750	2810 375	For each additional invention to be examined (37 CFR 1.129(b))	
1801 750	2801 375	Request for Continued Examination (RCE)	
1802 900	1802 900	Request for expedited examination of a design application	

Other fee (specify)

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) (\$1,110.00)

SUBMITTED BY

Name (Print/Type) John Hunt

Signature

Registration No. (Attorney/Agent)

36,424

(Complete if applicable)

Telephone 416.865.8121

Date

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Request and Payment Information

Description of Request and Payment Information 1. Extension Fee (3 month) and 2. Submission of IDS

Patent Fee	Patent Maintenance Fee	Trademark Fee	Other Fee
Application No. 09/668,482	Application No.	Serial No.	IDON Customer No.
Patent No.	Patent No.	Registration No.	
Attorney Docket No. 32391-2005		Identity or Describe Mark	

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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)		Docket Number (Optional) 32391-2005
In re Application of		
Application Number 09/668,482	Filed 09/25/2000	
For RETINOID METABOLIZING PROTEIN		
Art Unit 1652	Examiner SLOBODYANSKY, E.	

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows (check time period desired):

☐ One month (37 CFR 1.17(a)(1)) \$ _____

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☒ Three months (37 CFR 1.17(a)(3)) \$930.00

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☐ Five months (37 CFR 1.17(a)(5)) \$ _____

☐ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: \$ _____.

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☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).


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☐ attorney or agent under 37 CFR 1.34(a).
Registration number if acting under 37 CFR 1.34(a) _____

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August 11, 2003
Date

416.865.8121
Telephone Number


Signature

John C. Hunt
Typed or printed name

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)		Docket Number (Optional) 32391-2005
In re Application of		
Application Number 09/668,482		Filed 09/25/2000
For RETINOID METABOLIZING PROTEIN		
Art Unit 1652		Examiner SLOBODYANSKY, E.
This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.		
The requested extension and appropriate non-small-entity fee are as follows (check time period desired):		
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<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: \$ _____.		
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<input type="checkbox"/> assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).		
<input checked="" type="checkbox"/> attorney or agent of record. Registration Number 36,424		
<input type="checkbox"/> attorney or agent under 37 CFR 1.34(a). Registration number if acting under 37 CFR 1.34(a) _____		
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August 11, 2003 Date		 Signature
416.865.8121 Telephone Number		John C. Hunt Typed or printed name
NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.		
<input type="checkbox"/> Total of _____ forms are submitted.		

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Petkovich *et al.*
Serial No.: 09/668,482
Filing Date: September 25, 2000
Title: Retinoid Metabolizing Protein
Art Unit: 1652
Examiner: Elizabeth Slobodyansky, Ph.D.
Atty's Docket No.: 32391-2005

The Commissioner of Patents and Trademarks
Washington, D.C. 20331
U.S.A.

AMENDMENT

Dear Sir:

This is a response to the non-final office action of February 13, 2003.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

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LISTING OF CLAIMS

Claims 1 to 82 (previously cancelled)

83. (Currently amended) [An isolated] A microsomal preparation comprising a recombinant protein expressed by a cell that has been transfected with a nucleic acid molecule encoding the protein, or by a descendent cell thereof, [which] wherein said protein oxidizes [a retinoid] all-trans retinoic acid at the C4-position of the β -ionone ring, said [and encoded by a] nucleic acid molecule comprising a nucleotide sequence that hybridizes under high stringency conditions, wherein high stringency conditions include a wash step of about 0.2 x SSC at 50°C, to a polynucleotide having a nucleotide sequence selected from the group of sequences shown as: SEQ ID NO:3; [a sequence which varies from SEQ ID NO:3 in a coding region due to the degeneracy of the genetic code;] SEQ ID NO:5; [a sequence which varies from SEQ ID NO:5 in a coding region due to the degeneracy of the genetic code;] and SEQ ID NO:31; [a sequence which varies from SEQ ID NO:31 in a coding region due to the degeneracy of the genetic code, or a conservatively substituted amino acid variant of a said protein which oxidizes a retinoid] and wherein the microsomal preparation is substantially free of other proteins that are cytochromes expressed by epidermal cells.

Claims 84 to 89 (Cancelled)

90. (Currently amended) [An isolated] A microsomal preparation comprising a recombinant protein expressed by a cell that has been transfected with a nucleic acid molecule encoding the protein, or by a descendent cell thereof, [which] wherein said protein hydroxylates [a retinoid] all-trans retinoic acid at the C4-position [4-position] of the β -ionone ring, said [and encoded by a] nucleic acid molecule comprising a nucleotide sequence that hybridizes under high stringency

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conditions, wherein high stringency conditions include a wash step of about 0.2 x SSC at 50°C, to a nucleic acid molecule having a nucleotide sequence selected from the group of sequences shown as: SEQ ID NO:3; [a sequence which varies from SEQ ID NO:3 in a coding region due to the degeneracy of the genetic code;] SEQ ID NO:5; [a sequence which varies from SEQ ID NO:5 in a coding region due to the degeneracy of the genetic code;] and SEQ ID NO:31; [a sequence which varies from SEQ ID NO:31 in a coding region due to the degeneracy of the genetic code, or a conservatively substituted amino acid variant of a said protein which hydroxylates a retinoid] and wherein the microsomal preparation is substantially free of other proteins that are cytochromes expressed by epidermal cells.

Claims 91 to 112 (Cancelled)

113. (New) The preparation of claim 83, wherein said nucleotide sequence hybridizes under said conditions to SEQ ID NO:3.

114. (New) The preparation of claim 83, wherein said nucleotide sequence hybridizes under said conditions to SEQ ID NO:5.

115. (New) The preparation of claim 83, wherein said nucleotide sequence hybridizes under said conditions to SEQ ID NO:31.

116. (New) The preparation of claim 114, wherein the amino acid sequence identity between the protein and SEQ ID NO:4 is at least about 93 percent.

117. (New) The preparation of claim 116, wherein the protein comprises the amino acid sequence identified as SEQ ID NO:4.

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118. (New) The preparation of claim 113, wherein the protein comprises the amino acid sequence identified as SEQ ID NO:2.

119. (New) The preparation of claim 115, wherein the protein comprises the amino acid sequence identified as SEQ ID NO:32.

120. (New) The preparation of claim 83, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 35 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

121. (New) The preparation of claim 120, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 40 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

122. (New) The preparation of claim 121, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 50 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

123. (New) The preparation of claim 122 wherein the nucleic acid molecule encodes an amino acid sequence that is at least 60 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

124. (New) The preparation of claim 123, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 65 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

125. (New) The preparation of claim 124, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 70 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

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126. (New) The preparation of claim 125, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 75 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

127. (New) The preparation of claim 126, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 85 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

128. (New) The preparation of claim 127, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 90 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

129. (New) The preparation of claim 128, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 95 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

130. (New) The preparation of claim 83, wherein the protein hydroxylates the C18-position of *all-trans* retinoic acid.

131. (New) The preparation of claim 90, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 35 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

132. (New) The preparation of claim 131, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 40 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

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133. (New) The preparation of claim 132, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 50 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

134. (New) The preparation of claim 133, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 60 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

135. (New) The preparation of claim 134, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 65 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

136. (New) The preparation of claim 135, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 70 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

137. (New) The preparation of claim 136, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 75 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

138. (New) The preparation of claim 137, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 85 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

139. (New) The preparation of claim 138, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 90 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

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140. (New) The preparation of claim 139, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 95 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

141. (New) The preparation of claim 90, wherein the protein hydroxylates the C18-position of all-*trans* retinoic acid.

142. (New) A microsomal preparation comprising a recombinant protein expressed by a cell that has been transfected with a nucleic acid molecule encoding the protein, or by a descendent cell thereof, wherein said protein oxidizes all-*trans* retinoic acid at the C4-position of the β -ionone ring, said nucleic acid molecule encoding an amino acid sequence that is at least 60 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32, and wherein the microsomal preparation is substantially free of other proteins that are cytochromes expressed by epidermal cells.

143. (New) The preparation of claim 142, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 65 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

144. (New) The preparation of claim 143, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 70 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

145. (New) The preparation of claim 144, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 75 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

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146. (New) The preparation of claim 145, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 85 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

147. (New) The preparation of claim 146, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 90 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

148. (New) The preparation of claim 147, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 95 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

149. (New) The preparation of claim 142, wherein the protein hydroxylates the C18-position of *all-trans* retinoic acid.

150. (New) A microsomal preparation comprising a recombinant protein expressed by a cell that has been transfected with a nucleic acid molecule encoding the protein, or by a descendent cell thereof, wherein said protein hydroxylates *all-trans* retinoic acid at the C4-position of the β -ionone ring, said nucleic acid molecule encoding an amino acid sequence that is at least 60 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32, and wherein the microsomal preparation is substantially free of other proteins that are cytochromes expressed by epidermal cells.

151. (New) The preparation of claim 150, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 65 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

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152. (New) The preparation of claim 151, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 70 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

153. (New) The preparation of claim 152, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 75 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

154. (New) The preparation of claim 153, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 85 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

155. (New) The preparation of claim 154, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 90 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

156. (New) The preparation of claim 155, wherein the nucleic acid molecule encodes an amino acid sequence that is at least 95 percent conserved with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32.

157. (New) The preparation of claim 150, wherein the protein hydroxylates the C18-position of all-*trans* retinoic acid.

158. (New) The preparation of claim 83, wherein the preparation is enriched at least 6.3 fold in said oxidase activity with respect to a microsomal preparation obtained from a non-transfected said cell under the same conditions.

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159. (New) The preparation of claim 90, wherein the preparation is enriched at least 7.8 fold in said hydroxylase activity with respect to a microsomal preparation obtained from a non-transfected said cell under the same conditions.

160. (New) The preparation of claim 142, wherein the preparation is enriched at least 6.3 fold in said oxidase activity with respect to a microsomal preparation obtained from a non-transfected said cell under the same conditions.

161. (New) The preparation of claim 150, wherein the preparation is enriched at least 7.8 fold in said hydroxylase activity with respect to a microsomal preparation obtained from a non-transfected said cell under the same conditions.

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REMARKS

Claims 83, 90 and 113 to 161 are pending in the application.

No new matter has been added by the amendments submitted herein, as explained further below.

Claim 83, as it previously read, was rejected under 35 U.S.C. § 112, first paragraph. Claim 83 has been amended to require the presence of a protein which oxidizes all-*trans* retinoic acid at the C4-position of the β -ionone ring, as suggested in the first paragraph on page 5 of the outstanding Examiner's Report. Applicant believes this meets all concerns raised with respect to this claim under 35 U.S.C. § 112, first paragraph.

Claim 83, as it read previously, was rejected under 35 U.S.C. § 102(b) as being anticipated by each of Duell *et al.* (1992) and Duell *et al.* (1996). Claim 83 has been amended to require a microsomal preparation that includes a recombinant protein expressed by a cell that has been transfected with a nucleic acid molecule encoding the protein, or expressed by a descendent of such a cell. Further the claim requires that the microsomal preparation be substantially free of other proteins that are cytochromes expressed by epidermal cells. See, for example, Figure 13(a) of the application as filed.

None of the Duell *et al.* references teaches or suggests a nucleic acid or protein sequence and so cannot be used to obtain a preparation containing the recited recombinant protein. All of the Duell *et al.* references describe expression of a protein in epidermal (skin) cells only and the expression must be induced by exposure of those cells to retinoic acid. This is much different from Applicants'

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invention as claimed in this application, which, through the use of transfection, provides expression of a specific protein without the presence of other cytochromes normally present in skin cells. Moreover, induction of biological activity of this protein by retinoic acid is not required in the transfected cells. An advantage of Applicants' invention as claimed is, for example, in the area of screening drugs (page 9, line 26 to line 40 of the application as filed), where certainty of the identity and presence of the protein being targetted is reproducibly provided, absent contaminating proteins and activities normally present in skin cells. None of the preparations of Duell *et al.* can provide this certainty.

Claim 90, rejected along the same lines as claim 83, has been amended to be directed to a microsomal preparation comprising a recombinant protein which hydroxylates all-*trans* retinoic acid at the C4-position and also requires that the preparation be substantially free of other proteins that are cytochromes expressed by epidermal cells. For the reasons that Applicants believe that claim 83 is patentable over the Duell *et al.* articles and other art of record, Applicants believe that claim 90 is patentable.

Each of independent claims 142 and 150, new in the application, has been drafted to meet the requirements set out in the most recent action. Claim 142 requires the recited protein to oxidize all-*trans* retinoic acid at the C4-position of the β -ionone ring. Claim 150 requires the recited protein to hydroxylate all-*trans* retinoic acid at the C4-position of the β -ionone ring. Each claim also requires the recited protein to have a minimum amino acid sequence homology of 60 percent with respect to SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:32, and that the microsomal preparation be substantially free of other proteins that are cytochromes expressed by epidermal cells. Support for these claims can be found, for example, in the third paragraph on page 4 of the application as filed.

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The remaining claims, all of which are dependent claims, are being submitted for consideration by the Examiner. These claims recite features described in the application as filed, particularly in the third paragraph on page 4, and at line 6 of page 31. Example 1, on page 17 of the specification, describes BLAST search analyses which revealed less than 30 percent sequence homology between SEQ ID NO:2 (zP450RAI) and other previously known cytochrome P450s. Support for claims 158 to 161 is provided by Examples 6 and 7, and particularly Figures 11(a), 11(b) and 13(a).

Applicants note, as discussed in prior submissions, that the activity of the recited class of protein, and accordingly the claimed microsomal preparation, is not limited to that activity recited in the claims. Referring to Example 3, page 15, lines 10 to 11 of the application, "zP450 expression in COS-1 cells promoted the rapid conversion of RA into both lipid- and aqueous-soluble metabolites." This is evident in Figures 4(a) and 4(b), which are elution profiles of radioactively labelled, lipid-soluble RA metabolites of control and zP450RAI-transfected cells. The profiles clearly demonstrate that zP450RAI produces a significant amount (relative to control) of aqueous soluble metabolites other than (more polar than) RA, 4-OH-RA and 4-oxo-RA. Applicants discuss this in Example 3 (page 15, lines 20 to 23), as follows: "It is possible that the aqueous-soluble radioactivity represents glucuronides of RA metabolites or glucuronides of RA itself. Rapid glucuronidation of 4- and 18-hydroxy-RA in mammalian cell extracts has been reported by others [Wouters, 1992; Takatsuka, 1996]." Applicants thus reasonably expect that a member of the recited class of protein oxidizes the 18-position of the β -ionone ring as well as the 4-position, and that a said member oxidizes retinol as well as RA (see page 3, lines 23 to 26). In Example 5, Applicants describe on page 17 trials in which the metabolism of radioactively labelled RA by hP450RAI-transfected COS cells was examined.

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Results are shown in Figures 10(a), 10(b) and 10(c). All three panels of the figure show radioactive RA-derived metabolites not in the control. hP450RAI produced significant amounts of both aqueous and lipid soluble metabolites. Moreover, at least two unidentified metabolites (i.e., not 4-OH-RA or 4-oxo-RA) were produced. Applicants reasonably believe these to be other retinoid oxidation products. The protein recited in claim 83, for example, thus encompasses a protein that not only oxidizes the C4-position of retinoic acid, but also has other retinoid metabolizing activity.

Applicants make these amendments solely to advance prosecution of this application, and reserve the right to file a continuation or other application as appropriate in order to address otherwise outstanding issues.

Applicants believe that all of the issues addressed in the outstanding Action have been addressed in this response, and thus request allowance of the application.

Note Regarding Representation

The undersigned, an appointed agent of the Applicants, has recently changed firms. The new address and telephone number of the undersigned are indicated below. A change of address of the undersigned is on record with the PTO. A Power of Attorney appointing practitioners under the same PTO Customer Number as the undersigned will be submitted in due course.

In the event that any issue remains, or if the Examiner is disposed to issue an unfavorable final action, the Examiner is invited to telephone the undersigned at (416) 865-8281.

Application No .09/668,482
Amendment dated August 11, 2003
Reply to Actl n f February 13, 2003

- 15 -

A petition for extension of time for submitting this response, and an authorized Visa Credit Card, Form PTO 2038 accompany this response. Applicants hereby request any further extension of time that may be necessary. Please charge any additional fees which may be required for the papers being filed with this letter to our authorized Visa Credit Card. In the event that charges cannot be made to the authorized credit card, please charge any fee to Deposit Account No. 502651.

Yours very truly,



John C. Hunt
Registration No. 36,424

August 11, 2003
Date

Torys LLP
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79 Wellington Street West
Box 270, TD Centre
Toronto, Ontario
M5L 1A9
Canada

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Petkovich *et al.*
Serial No.: 09/668,482
Filing Date: September 25, 2000
Title: Retinoid Metabolizing Protein
Art Unit: 1652
Examiner: Elizabeth Slobodyansky, Ph.D.
Atty's Docket No.: 32391-2005

The Commissioner of Patents and Trademarks
Washington, D.C. 20331
U.S.A.

Dear Sir:

This is a submission under 37 C.F.R. § 1.56.

Applicants would like to bring to the attention of the Examiner the enclosed reference entitled, "Retinoic Acid Isomers Applied to Human Skin *in Vivo* Each Induce a 4-Hydroxylase That Inactivates Only *Trans* Retinoic Acid," by Duell *et al.* published in the February 1996 issue of The Journal of Investigative Dermatology.

The Examiner's attention is drawn, in particular, to Figure 1 which shows the time course for induction of RA-4 hydroxylase activity after topical application of 0.1% *t*-RA cream to adult human skin under occlusion.

Yours very truly,



John C. Hunt
Registration No. 36,424

August 11, 2003
Date

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PTO/SB/08B (02-03)

Approved for use through 04/30/2003. OMB 0851-0031

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Substitute for form 1449/PTO

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**

(Use as many sheets as necessary)

Complete if Known

Application Number	09/668,482
Filing Date	09/25/2000
First Named Inventor	PETKOVICH, Martin P.
Art Unit	1652
Examiner Name	SLOBODYANSKY, Elizabeth
Attorney Docket Number	32391-2005

Sheet

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of

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OTHER PRIOR ART—NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		ELIZABETH A. DUELL, SEWON KANG, and JOHN J. VOORHEES, Retinoic Acid Isomers Applied to Human Skin in Vivo Each Induce a 4-Hydroxylase That Inactivates Only Trans Retinoic Acid (The Journal of Investigative Dermatology - pgs. 316-320 - Vol. 106, No. 2	

Examiner
SignatureDate
Considered

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 120 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Washington, DC 20231.

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Retinoic Acid Isomers Applied to Human Skin *in Vivo* Each Induce a 4-Hydroxylase That Inactivates Only *Trans* Retinoic Acid

Elizabeth A. Duell, Sewon Kang, and John J. Voorhees

Department of Dermatology, University of Michigan Medical School, Ann Arbor, Michigan, U.S.A.

Application of all-*trans* retinoic acid to human skin for 4 d under occlusion produces a marked increase in retinoic acid 4-hydroxylase activity. In this study, the possible induction of other hydroxylases in response to 9-*cis* and 13-*cis* retinoic acid applications to adult human skin *in vivo* was determined. Application of 0.1% all-*trans*, 0.1% 9-*cis*, and 0.1% 13-*cis* retinoic acid to human skin for 2 d resulted in induction of only all-*trans* retinoic acid 4-hydroxylase activity. The 4-hydroxylase activity in microsomes from the treated tissue ranged from 383 ± 46 to 531 ± 59 pg of 4-hydroxy all-*trans* retinoic acid formed/min/mg protein ($n = 6$). These same preparations were unable to use 9-*cis* or 13-*cis* retinoic acid as substrate for the hydroxylation reaction. Extraction of the retinoic acid isomers from epidermis 48 h after application of 0.1% solution of each

isomer yielded significant amounts of all-*trans* retinoic acid (36–72%) regardless of the isomer applied. The all-*trans* isomer produced by isomerization of both 9-*cis* and 13-*cis* retinoic acids is the likely inducer of the 4-hydroxylase. All-*trans* retinol and all-*trans* retinal were unable to compete with all-*trans* retinoic acid as substrate for 4-hydroxylase enzymes. The 4-hydroxylase induced in response to pharmacological doses of retinoic acids is specific for the all-*trans* isomer. The inability of 9-*cis* or 13-*cis* retinoic acid to induce their own hydroxylation and inactivation or act as substrate for the 4-hydroxylase in skin may have considerable implications in light of the clinical use of retinoids in the treatment of various diseases including cancer. **Key words:** metabolism/isomerization/pharmacology/psoriasis P450. *J Invest Dermatol* 106:316–320, 1996

When human [1] or rat skin [2] is treated topically with all-*trans* retinoic acid (*t*-RA), a marked induction of RA 4-hydroxylase occurs. Because this hydroxylase may limit the activity of *t*-RA, 9-*cis* RA, and 13-*cis* RA, we investigated the time course for induction of RA hydroxylase, the specificity of the enzyme with the three isomers of RA, retinol (ROL), and retinaldehyde (RAL) as substrates, and possible induction of other hydroxylases in response to the topical application of 9-*cis* RA or 13-*cis* RA.

MATERIALS AND METHODS

Isocitrate, isocitrate dehydrogenase, NADP, 13-*cis* RA, *t*-RA, 13-*cis* RAL, 9-*cis* RAL, *t*-RAL, 13-*cis* ROL, and *t*-ROL were purchased from Sigma Chemical Co. (St. Louis, MO). Trifluorated *t*-RA, and ³H-*t*-ROL were obtained from DuPont NEN (Boston, MA). 9-*cis* RA, 9-*cis* ROL, ³H-9-*cis* RA, ³H-13-*cis* RA were gifts from Drs. Joseph Grippo, Arthur Levin, P.F. Sotter, and A.A. Liehman of Hoffmann La Roche Co. (Nutley, NJ). RA metabolites, 4-OH *t*-RA, 4-oxo *t*-RA, 4-oxo-13-*cis* RA, and 5,6-epoxy

RA, were gifts from Dr. Michael Rosenberger and P.F. Sotter of Hoffmann La Roche. All-*trans* RA 0.1% (Retin-A) and cream vehicle were supplied by Ortho Pharmaceutical Corp. (Raritan, NJ). High-performance liquid chromatography (HPLC) grade solvents were used for extraction and chromatographic solvents. Spherisorb ODS-1 columns were obtained from Pharm Separations (Norwalk, CT).

Application of Compounds and Biopsy Procedures Solutions of ROL (1.0%), *t*-RA (0.1%), 13-*cis* RA (0.1%) and 9-*cis* RA (0.1%) were prepared in a vehicle consisting of 95% ethanol and propylene glycol (7:3, vol/vol) containing 0.5 mg butylated hydroxytoluene/ml of solution (BHT). The use of BHT as vehicle was required since only *t*-RA was available in cream base used in the initial studies [1]. These solutions and vehicle were applied topically to a 1 × 2-inch area on the buttocks. The area is occluded and kept dark for indicated periods of time, usually 2 or 4 d. The 4-d time point gave consistent clinical evaluations and was the time selected in the initial studies. The 2-d time point, however, is adequate for biochemical studies without clinical correlations. The treated areas were infiltrated with 1% lidocaine local anesthesia and keratomed epidermal tissue (0.1-mm depth) was immediately frozen in liquid nitrogen and stored at -70°C until used. All subjects gave informed, written consent. The study was approved by the University of Michigan Medical Center Institutional Review Board.

Extraction of Retinoids Biopsy sites were tape stripped to glancing prior to biopsy to remove any retinoid trapped in dead stratum corneum that was not absorbed into the viable layers of the skin. Procedures were as previously stated [1]. Briefly, frozen keratome biopsies were ground to a powder under liquid nitrogen with a mortar and pestle. The material was quickly transferred to a homogenizer containing the extraction solvent (chloroform and methanol [2:1]) with tracer ³H-*t*-RA (to estimate recovery) and was homogenized. After two additional extractions, the organic phase was evaporated, resuspended, filtered, and injected onto the HPLC column. Protein determinations were by the method of Lowry *et al* [3] with bovine serum albumin as a standard.

Manuscript received February 24, 1995; revised September 27, 1995; accepted for publication October 16, 1995.

This work was presented in part at the annual meeting of the Society for Investigative Dermatology, Baltimore, Maryland (April 27–30, 1994).

Reprint requests to: Dr. Elizabeth A. Duell, University of Michigan Medical Center, Department of Dermatology, R 6558 Kraseg 1, Box 0528, Ann Arbor, MI 48107-0528.

Abbreviations: *t*-RA, all-*trans* retinoic acid; 9-*cis* RA, 9-*cis* retinoic acid; 13-*cis* RA, 13-*cis* retinoic acid; ROL, retinol; RAL, retinaldehyde; EPG, 95% ethanol; propylene glycol (7:3, vol/vol) with 0.5 mg butylated hydroxytoluene/ml.

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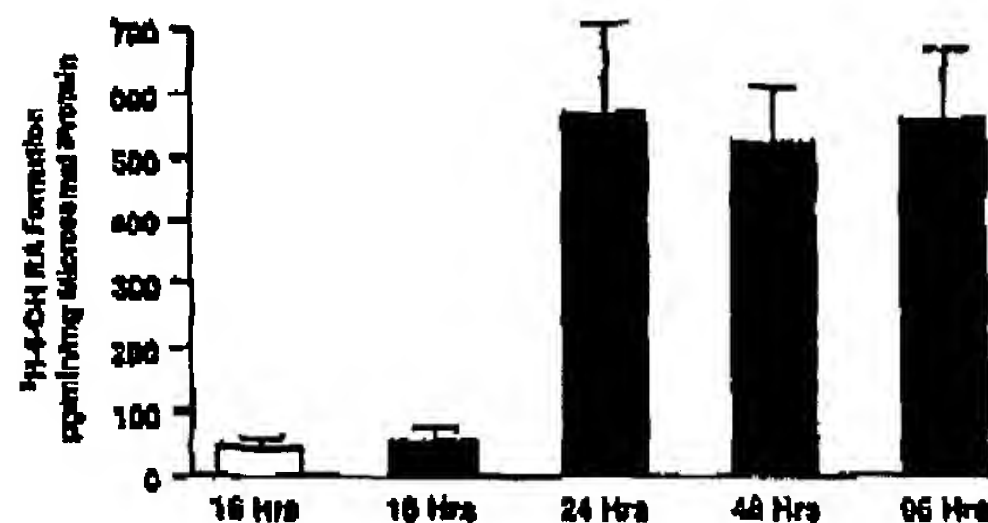


Figure 1. Time course for induction of RA-4 hydroxylase activity after topical application of 0.1% *t*-RA cream to adult human skin under occlusion. ^3H -*t*-RA (2 μM) and an NADPH regenerating system was incubated *in vitro* with microsomes from tissues treated *in vivo* with *t*-RA cream. Other assay conditions and separation of metabolites are given in Materials and Methods. \square , vehicle; \blacksquare , samples from *t*-RA sites treated for the times indicated. The number of individual subjects from whom microsomes were prepared at the indicated time points are as follows: $n = 6$ for vehicle and *t*-RA treated for 16 and 24 h; $n = 8$ for 48 h; $n = 5$ for 96 h. Error bars, SEM, for each series.

Enzyme Assays Microsomal fractions were prepared as previously described [1]. RA and RA metabolites were kept in amber glass in darkened rooms with yellow lighting. The rate of RA metabolism was determined by incubating 100 μg microsomal protein in 0.01 M phosphate buffer, pH 7.4, containing an NADPH regenerating system and ^3H -*t*-RA or other tritiated retinoids as substrates. Samples were incubated for 30 min at 35°C. The activity is expressed as picograms of 4-OH RA formed per minute per milligram of microsomal protein. Compounds tested as possible competitive substrates were added to the assay mix just prior to the addition of ^3H -*t*-RA. The reaction was terminated by addition of 100 μl of methanol cooled to -20°C.

HPLC Separation An HPLC system (1090M; Hewlett-Packard Co., Palo Alto, CA) containing a Spherisorb ODS-1 column (25 \times 4.6 mm), a diode array detector and a chem workstation was used to separate and quantitate retinoids and metabolites [1]. The standard compounds used to calibrate the column contained the following retinoids: 4-OH RA; 4-oxo-13-*trans*-RA; 4-oxo-*t*-RA; 5,6-epoxy RA; 13-*cis*-RA; 9-*cis*-RA; *t*-RA; 13-*cis*-ROL; *t*-ROL; 13-*cis*-RAL; *t*-RAL. A gradient elution system separated the retinoids and metabolites in a 42-min time period. Effluent from the HPLC column flowed directly into a flow through scintillation counter (Flow-Ona Beta model 295A, Packard Instrument Co., Meriden, CT) with a computerized data capture system to determine radioactivity in each peak. The amount of metabolite formed was calculated based on the specific activity of added [^3H]retinoid.

RESULTS

Time Course of RA 4-Hydroxylase Induction in Microsomes Isolated from Human Skin Following *In Vivo* Application of 0.1% *t*-RA A marked induction of *t*-RA 4-hydroxylase was reported after human skin had been exposed to 0.1% *t*-RA continuously for 4 d under occlusive patch [1]. Figure 1 shows that in comparison to cream base only (45 \pm 13 pg/min/mg microsomal protein), no RA 4-hydroxylase induction occurred at 16 h after application of *t*-RA in cream base (56 \pm 18 pg/min/mg protein). In data not shown, there is no significant difference in 4-hydroxylase activity in cream base only treated areas in comparison to areas receiving no treatment. The baseline RA 4-hydroxylase activity varies with different individuals from barely detectable to moderate activity. Twenty-four hours after a single application of *t*-RA in cream base, a 10-fold induction of RA 4-hydroxylase activity (569 \pm 142 pg/min/mg protein) had occurred. Similar activities were maintained 48 or 96 h after application of *t*-RA, as shown in Fig 1. The time lag of greater than 16 h but less than 24 h for the increase in RA 4-hydroxylase activity includes the time required for penetration of the *t*-RA, activation of gene transcription, and mRNA and protein synthesis.

METABOLISM OF RETINOIC ACIDS IN SKIN 517

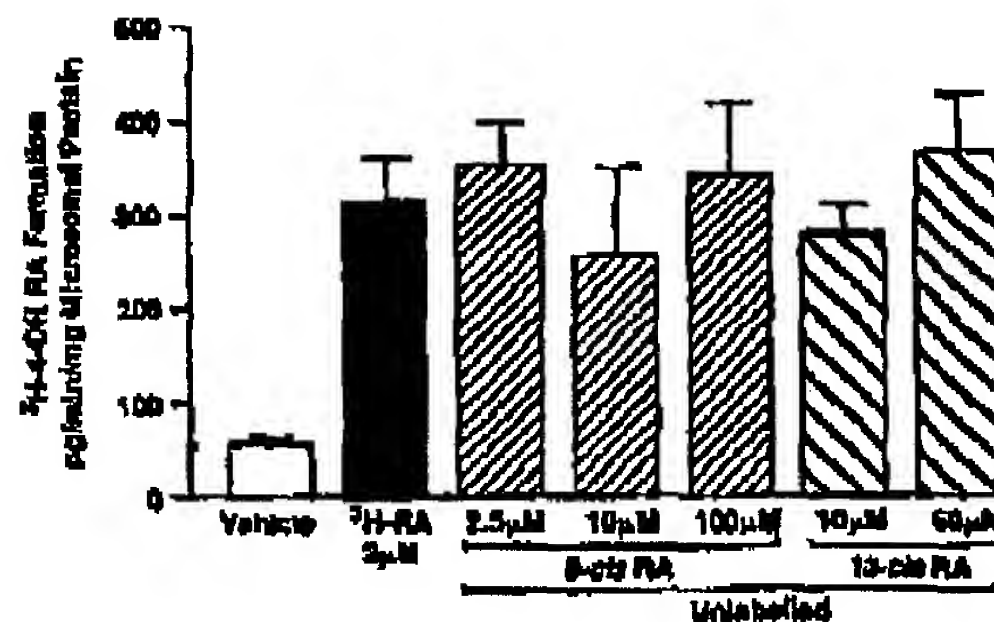


Figure 2. 9-*cis* RA and 13-*cis* RA isomers of *t*-RA are not substrates for RA 4-hydroxylase activity induced by topical application of 0.1% *t*-RA cream. Assay conditions are given in legend to Fig 1 except for the addition of the unlabeled isomers. The number of microsomal fractions used are as follows: vehicle ($n = 3$), and ^3H -*t*-RA ($n = 13$); for added 9-*cis* RA—2.5 μM ($n = 7$), 10 μM ($n = 3$), and 100 μM ($n = 6$); for added 13-*cis* RA—10 μM ($n = 3$) and 60 μM ($n = 6$). Error bars, SEM. Using Student's *t* test for paired samples, there was no significant difference in 4-OH RA formation in the presence or absence of RA isomers ($p > 0.5$).

9-*cis* RA and 13-*cis* RA as Substrates for RA-4-Hydroxylase in Skin To test whether or not the all-*trans* configuration was necessary for RA to be a substrate for the induced enzyme, nonradioactive 9-*cis* and 13-*cis* RA were added as competitive substrates for the ^3H -*t*-RA in the standard *in vitro* assay. The data are given in Fig 2. The ^3H -*t*-RA concentration was 2 μM with 4-OH *t*-RA formation of 315 \pm 46 pg/min/mg protein. The addition of nonradioactive 2.5 μM 9-*cis* RA, 10 μM 9-*cis* RA, or 100 μM 9-*cis* RA did not significantly decrease the amount of ^3H -4-OH *t*-RA formed (average of 317 pg/min/mg protein for all 9-*cis* RA concentrations). Figure 2 also shows that similar results were obtained if nonradioactive 10 μM 13-*cis* RA or 60 μM 13-*cis* RA were present in the assay (average of 323 pg/min/mg protein for both concentrations of 13-*cis* RA). Thus, neither 9-*cis* RA nor 13-*cis* RA were able to compete with *t*-RA as substrate for the enzyme reaction.

In contrast, Fig 3 shows that the addition of unlabeled *t*-RA to 2 μM ^3H -*t*-RA decreased the DPM present in the 4-OH *t*-RA and this decrease was proportional to the decrease in specific activity of the ^3H -*t*-RA. Based on the specific activity of the substrate, there is no change in enzymatic activity (751 \pm 122 pg/min/mg protein).

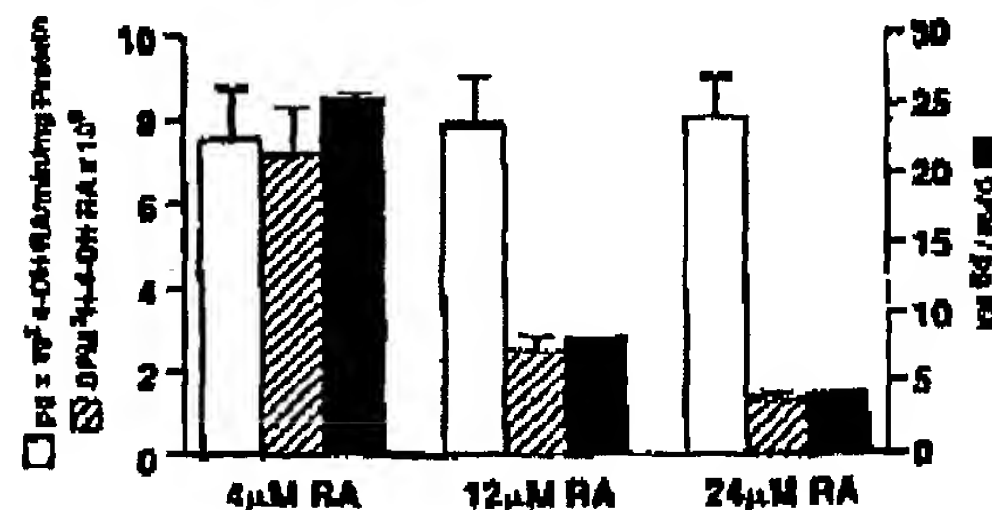
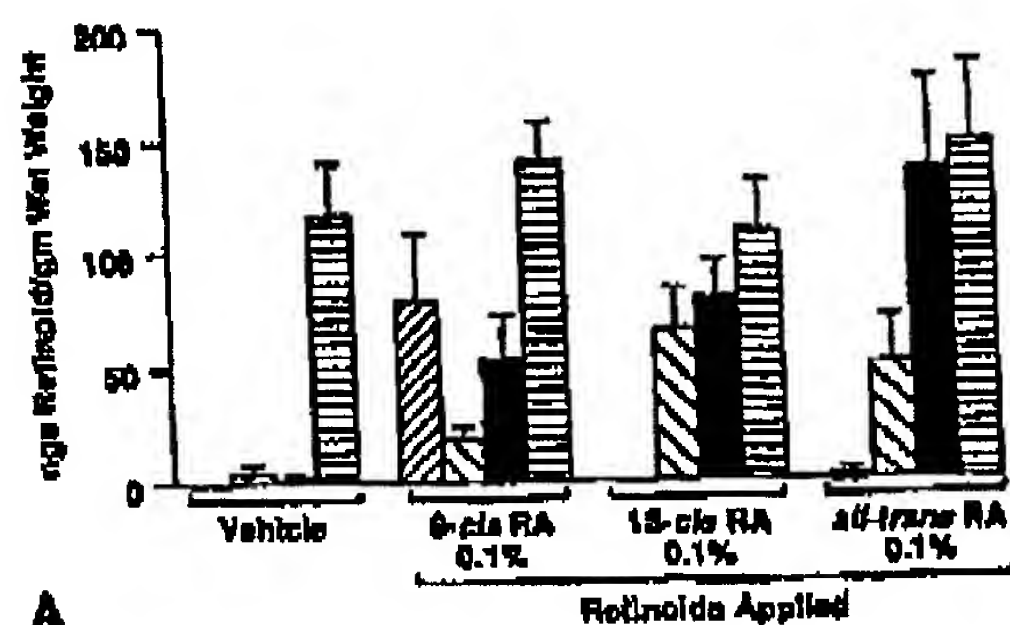
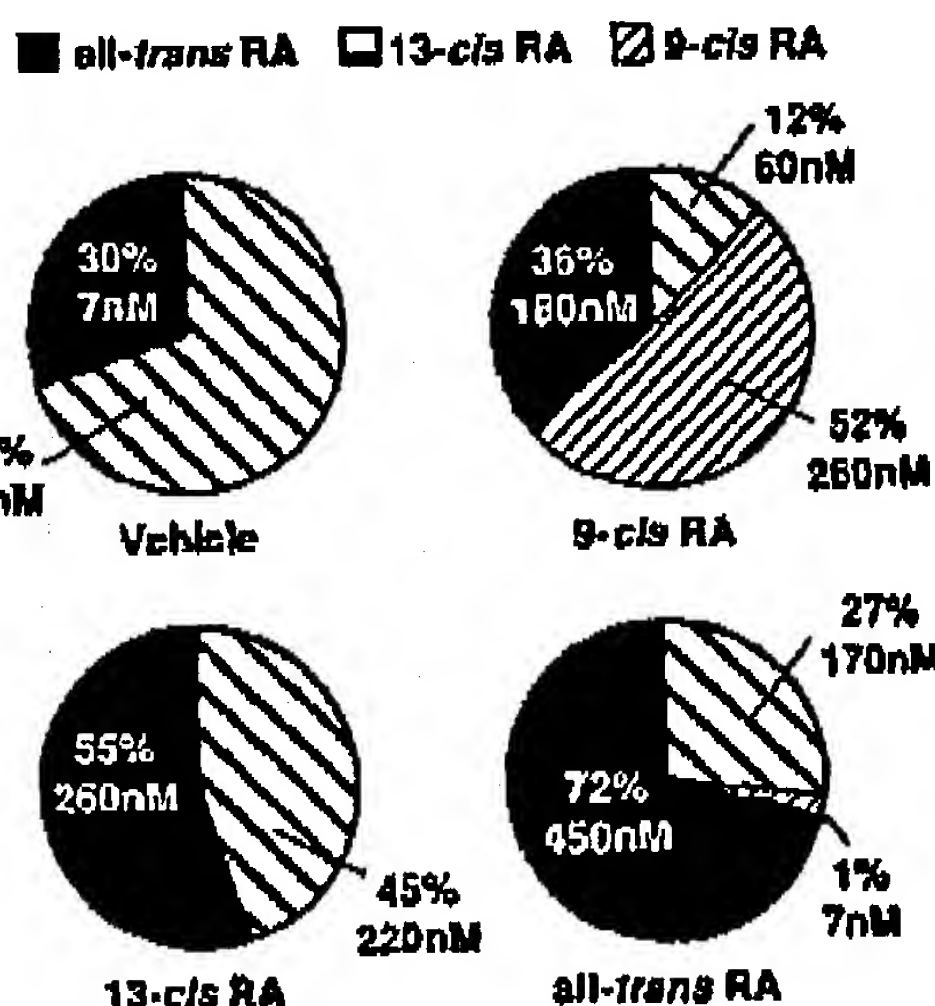


Figure 3. Addition of unlabeled *t*-RA decreases the formation of ^3H -4-OH *t*-RA but not the quantity of 4-OH *t*-RA. Assays were as given in legend to Fig 1 except additional unlabeled *t*-RA was added. Formation of 4-OH *t*-RA (pg) was calculated based on specific activity of added substrate. Microsomes were prepared from human skin treated *in vivo* with 0.1% *t*-RA cream ($n = 3$). Error bars, SEM.

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A



B

Figure 4. Quantities of 9-cis RA, 13-cis RA, and t-RA extracted from human skin following *in vivo* application in EPG of 0.1% of each isomer for 48 h at different sites on the same individuals. A) Nanograms per gram wet weight of each RA isomer and t-ROL extracted from the skin. The stratum corneum was stripped prior to keratinizing. Extracted material from treated areas: vehicle (□); 9-cis RA (▨); 13-cis RA (▩); with t-RA (■); ROL (◻). Error bars, SEM (n = 7). B) The percentage of each isomer was calculated based on the sum of nanograms of extracted RAs from each site as 100%. One gram of tissue = 1 ml was used to calculate nanomolar.

at 4 μ M RA, 785 ± 112 pg/min/mg protein for 12 μ M RA, and 800 ± 96 pg/min/mg protein for 24 μ M RA).

Extraction of RA Isomers Present in Epidermis 48 h After *In Vivo* Application of Vehicle, 9-cis RA, 13-cis RA and t-RA to Human Skin. All three RA isomers are soluble in EPG at a concentration of 0.1%. Two days after application of vehicle (EPG) and the three RA isomers in EPG to four different sites under occlusion on the buttock, the stratum corneum (outer layers of the skin) was removed by tape stripping. This was necessary in order to avoid erroneously high values for RA content in the viable layers due to unabsorbed material remaining on the surface of the skin.

Retinoic acids were extracted from the stripped, keratinized tissue and the amount of each RA isomer determined. These data are presented in Fig 4A,B. The bar graph in Fig 4A displays the

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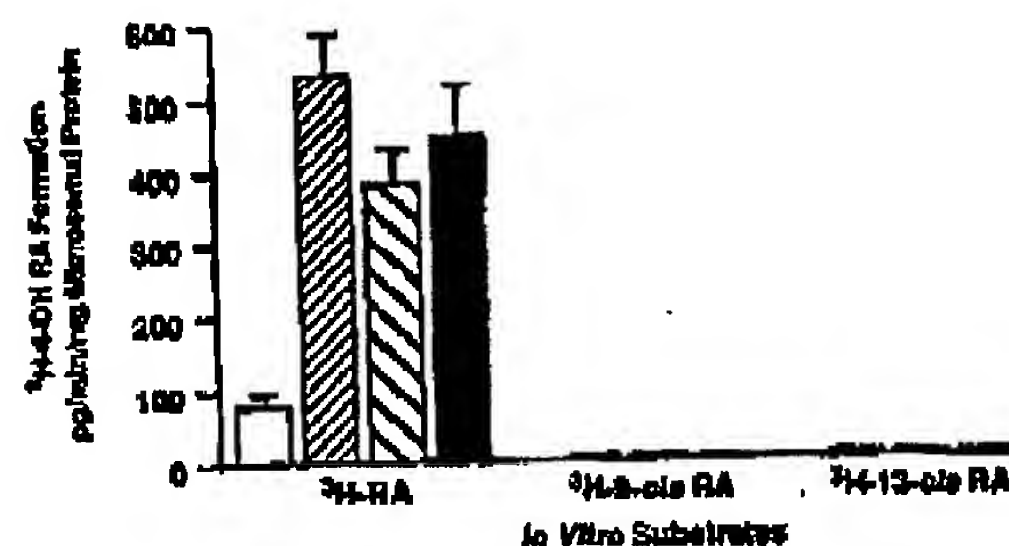


Figure 5. All-trans RA 4-OHase activity induced in human skin 48 h after *in vivo* application of 9-cis RA, 13-cis RA, or t-RA. Unlabeled RA isomers were applied *in vivo* in EPG solution for 48 h. All three tritiated isomers were used as substrates in the *in vitro* assay. Assay procedures given in legend to Fig 1 and in Materials and Methods. Error bars, SEM, for seven different microsomal preparations: vehicle (□); with 9-cis RA (▨); with 13-cis RA (▩); with t-RA (■).

nanograms per gram wet weight of each RA isomer extracted from each of the treated areas. The sum of the nanograms for the three RA isomers for each treated site is defined as 100%. The individual isomers extracted from a given site are expressed as a percentage of the sum and displayed in pie chart form in Fig 4B. Molar concentration of each RA isomer is also given for the four treated sites in Fig 4B. The total nanograms of the three isomers of RA extracted from the epidermis at each treated site were similar (145–188 ng RAs/g wet weight of tissue). All-trans RA (solid bar) was the most stable isomer with 72% of the applied isomer remaining as t-RA and achieved a concentration within epidermis of 0.45 μ M. A significant portion of total retinoic acids extracted from the tissue was t-RA regardless of the isomer applied (36% in 9-cis RA application areas, 55% in 13-cis RA application areas, and 72% in t-RA application areas). 9-cis RA (hatched bar) was recovered from 9-cis RA-treated areas (52%) and from t-RA-treated areas (1%), but none was detected in the 13-cis RA-treated areas. 13-cis RA (wide hatched bar) was recovered from all of the treated areas.

Induction of 4-Hydroxylase Activity in Epidermis 48 h After *In Vivo* Application of Vehicle, 9-cis RA, 13-cis RA, and t-RA to Human Skin. In a second series, the same solutions of the three RA isomers were applied and kept occluded for 2 d. Since RA isomers remaining on the surface would not interfere with either the microsomal preparation or the *in vitro* assay, the stratum corneum was not removed by tape stripping prior to the keratinase procedure. The results of the *in vitro* assays for RA 4-hydroxylase activity are depicted in Fig 5. With 3 H-t-RA as substrate, 4-OH t-RA was formed by microsomal fractions from areas treated with each of the three isomers. The activity associated with 9-cis RA treated areas was 531 ± 59 pg/min/mg protein and with 13-cis RA 349 ± 68 pg/min/mg protein and with t-RA 448 ± 68 pg/min/mg protein (n = 7). The vehicle value was 70 ± 16 pg/min/mg protein (n = 7). With 3 H-9-cis RA or 3 H-13-cis RA as substrate, no hydroxylated products were formed since no new peaks of radioactivity were detected in the region where more polar compounds elute (i.e., compounds with retention times earlier than 13-cis RA [28 min]).

Application of t-ROL Increases RA 4-Hydroxylase Activity. A solution of 1.6% t-ROL in EPG was applied to adult human skin for 4 d under occlusion. Microsomal fractions were prepared from these treated areas and were incubated *in vitro* with 3 H-t-ROL or 3 H-t-RA as substrate. As shown in Fig 6, the application of t-ROL or t-RA induced the t-RA 4-hydroxylase activity based on the *in vitro* assay with 3 H-t-RA as substrate. All-trans RA was a much

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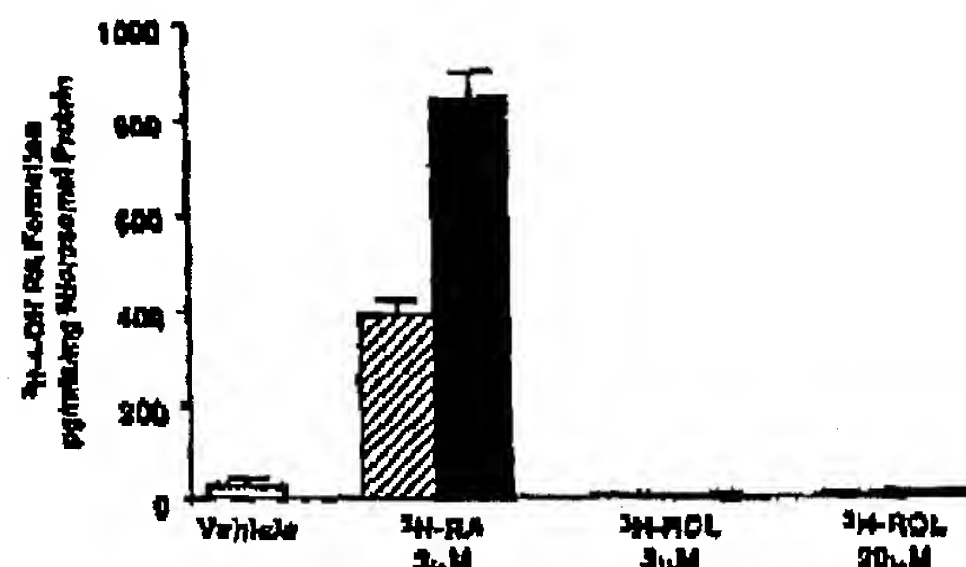


Figure 6. All-trans RA 4-OHase activity induced in human skin 96 h after application of 1.6% t-ROL or 0.1% t-RA. Tritiated t-RA or t-ROL were substrates in the assay of microsomes obtained from areas treated *in vivo* with t-RA or t-ROL in EPG solution. Error bars, SEM ($n = 5$ for ³H-t-ROL as substrate; $n = 4$ for ³H-t-RA as substrate). □, vehicle; ▨, 0.1% t-RA; ▩, 1.6% t-ROL.

more efficient inducer of RA 4-hydroxylase (841 ± 58 pg/min/mg microsomal protein, $n = 4$) in comparison to t-ROL (391 ± 32 pg/min/mg protein, $n = 5$). The rate of hydroxylation of t-RA in microsomes from vehicle-treated areas was 28 ± 17 pg/min/mg protein ($n = 4$). When microsomal fractions prepared from the ROL-treated areas were assayed for ROL hydroxylase activity, there was no formation of ³H-4-OH ROL since no radioactive peaks were detected at retention times consistent with polar metabolite formation even at a substrate concentration of $20 \mu\text{M}$ ³H-t-ROL. Although 4-OH ROL can be oxidized to additional metabolites in other tissues, no unidentified peaks were present in the chromatograms from these incubations.

Other retinoids tested for their capacity to function as alternative substrate were the other two ROL isomers and the three corresponding RAL isomers. These retinoids ($20 \mu\text{M}$) were added to the standard *in vitro* assay containing ³H-t-RA, which resulted in a 7-fold excess of ROLs or RALs compared with ³H-t-RA. The microsomes used in the *in vitro* assays were obtained from areas treated with 0.1% t-RA. As shown in Fig 7, there was a 10-fold induction of 4-hydroxylase activity 765 ± 67 pg/min/mg microsomal protein ($n = 18$) for the t-RA treated areas compared with 63 ± 14 pg/min/mg protein ($n = 18$) for vehicle-treated areas. There were no significant decreases in the amount of ³H-4-OH t-RA formed by the addition to the assay of any retinol or retinal isomer. The activity in the presence of $20 \mu\text{M}$ t-ROL or t-RAL was 700 ± 101 pg 4-OH t-RA/min/mg protein ($n = 6$) or 938 ± 148 pg/min/mg protein ($n = 6$). These values are not significantly different from t-RA alone.

DISCUSSION

The clinical use of retinoids t-RA and 13-cis RA in topical preparations circumvents one of the cell's control points (the rate of synthesis of LAAs) for maintaining the necessary concentration of t-RA. Metabolism of the added retinoids to less active metabolites is one of the mechanisms that can be used to limit effects of topically applied retinoids. While little is known about the specifics of retinoid metabolism and inactivation in skin, the induction of a 4-hydroxylase activity in response to topical application of t-RA is known [1,2]. A major metabolite of 13-cis RA found in blood following oral administration is 4-oxo-13-cis RA [4], a stable 4-hydroxylated metabolite of 13-cis RA. *In vitro* incubation of 13-cis RA with a 9,000g supernatant fraction from rat liver produced the same metabolite [5]. Hydroxylation may be the main mechanism for inactivation of RAAs. The possibility existed that the cytochrome P450 4-hydroxylase induced in response to t-RA in skin might also hydroxylate the other isomers (i.e., 9-cis RA and 13-cis RA) in skin.

METABOLISM OF RETINOIC ACIDS IN SKIN 319

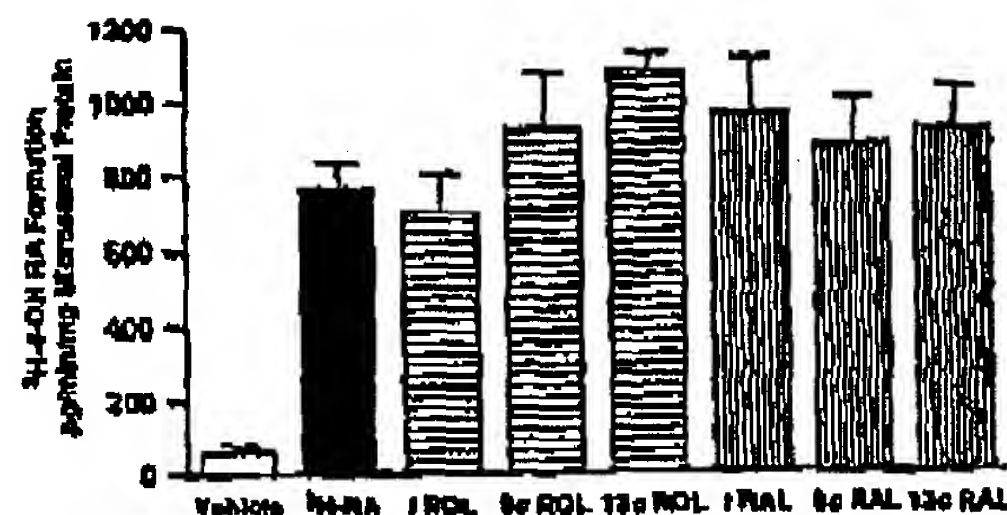


Figure 7. Three isomers of ROL and RAL do not compete with the transformation of ³H-t-RA to 4-OH RA *in vitro* with microsomes obtained from areas exposed to 0.1% t-RA cream *in vivo* for 96 h. Assays components as given in legend to Fig 1. Unlabeled 9-cis, 13-cis, and all-trans isomers of retinol ($20 \mu\text{M}$) and retinal ($20 \mu\text{M}$) were added to the *in vitro* assay in a 7-fold excess of the substrate ³H-t-RA. Error bars, SEM ($n = 18$ for assays with vehicle or ³H-t-RA alone; $n = 6$ for all other experiments given).

The data demonstrate that the 4-hydroxylase induced following application of t-RA is specific for t-RA. Since retinoids are known to isomerize with exposure to air and light, the stability of each isomer during penetration into the viable layers of the skin was determined. The results show that t-RA was the most stable of the three isomers and that regardless of the isomer of RA applied, at least 40–50% of the RA in the viable layers of the epidermis is isomerized to t-RA. These data are consistent with recent data obtained with rat liver microsomes *in vitro* [6]. In the report, 40–50% of the added 13-cis RA was converted into t-RA after a 30-min incubation at 37°C whereas only 11% of added t-RA was isomerized into 13-cis RA.

The isomerization of the applied 9-cis RA and 13-cis RA to t-RA in the skin would explain the observed induction of the t-RA 4-hydroxylase in the epidermis regardless of the isomer applied. A sufficient level of t-RA was formed by isomerization of 9-cis and 13-cis RA so that the same results were produced as if t-RA had been applied (i.e., induction of t-RA 4-hydroxylase). It is also important to note that neither 9-cis RA nor 13-cis RA were able to induce a hydroxylase activity in skin that would result in inactivation of these isomers.

Liver, however, does appear able to metabolize 13-cis RA by hydroxylation. Experiments with mice showed that feeding 13-cis RA increased elimination of 13-cis RA only in liver, whereas feeding t-RA increased the elimination of t-RA in all tissues studied [7]. In other studies microsomal preparations from mouse liver but not mouse skin were able to hydroxylate 13-cis RA in an *in vitro* assay system [8].

In human liver cytochrome P450 2C8 hydroxylates not only t-RA but also t-ROL [9] and rabbit liver P450 2B4 and 1A2 hydroxylate both t-ROL and t-RAL [10]. Both of these studies were carried out with purified cytochrome P450s. Since topical application of ROL to adult human skin produces many of the same effects as RA [11], we determined whether t-ROL could induce a t-ROL and/or t-RA 4-hydroxylase. Since conversion of ROL to RA may be necessary for induction of RA 4-hydroxylase activity, a much higher concentration of ROL was used to assure adequate penetration and conversion to RA. Topical application of 1.6% ROL, a concentration 10-fold > t-RA, did induce RA 4-hydroxylase activity, but to a lesser extent, 46.5% of that achieved with 0.1% t-RA. In contrast to the P450s in liver, however, the skin P450 induced by t-ROL did not hydroxylate t-ROL as indicated by a lack of conversion of ³H-ROL to more polar compounds in the *in vitro* assay system. While 4-OH ROL is less stable than 4-OH RA, the formation of 4-OH ROL with skin at the enzyme source should have been detected if formed since in

in vitro assay system was similar to that used to detect 4-OH ROL with liver as the enzyme source [9,10].

The skin appears to tightly control its *t*-RA levels by strict limitation of its formation from ROL and by specific inactivation through 4-hydroxylation. Skin does not appear, however, to have a direct means of controlling 13-*cis* or 9-*cis* RA levels after topical application, other than isomerization to *t*-RA or possibly glucuronidation.

Inactivation of applied 13-*cis* RA could be absorption into the blood stream and transport to the liver for conversion to 4-OH-13-*cis* RA by only cytochrome P4502C8 found in liver [9]. Such an inactivation, however, if it occurs in liver, would not be clinically important because topical application of *t*-RA and 13-*cis* RA in man produces slight and variable changes in blood levels of these retinoids [12,13]. Therefore, local inactivation in the skin of topically applied, naturally occurring stereoisomers of RA via a final common isomerization pathway to *t*-RA and subsequent 4-hydroxylation appears to be a critical detoxification mechanism in skin. At the present time little is known about the which P450 associated enzyme carries out this reaction in skin. The use of substrates and inhibitor specific for a P450 enzyme family has not shed light on this question (unpublished data). Likewise, the presence of CRABP I or II in the assay did not alter the rate of RA 4-hydroxylation (unpublished results).

Lastly, the kinds of experiments described in this article are difficult to perform in noncutaneous tissues. Nonetheless, should other tissues be similar to skin in their capacity to convert 9- and 13-*cis* RA to *t*-RA for inactivation, the mechanisms described here may have considerable implications for the treatment of systemic diseases such as aerodigestive tract cancer and acute promyelocytic leukemia with the natural isomers of RA [14,15].

The authors thank Robin Gardner for her expertise in applying the compounds, removing of stratum corneum with tape stripping when required, and keratinizing of the treated areas. We are also indebted to Judith Schmitt for her technical expertise and Laura Van Cael for the illustrations. Simon Kong acknowledges the support of Dermatology Foundation.

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09/668,482	09/15/2000	P. Martin Petkovich	57600/00095	3039

7590 08/19/2003
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	First Named Inventor	PETKOVICH, Martin P.
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Please address all correspondence and telephone calls to:

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Canada
Phone 416-865-7500
Facsimile 416-865-7380

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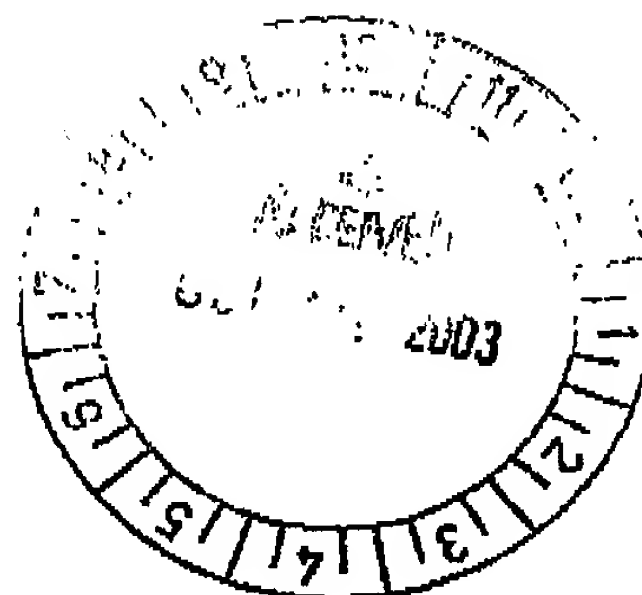
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